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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,297	01/24/2005	Matthew Baker	MER-137	9233

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,297	BAKER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 21-38* is/are pending in the application.

4a) Of the above claim(s) *22,23,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21,24,25 and 28-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 24 January 2005 has been entered. Claims 2-20 were canceled. New claims 21-37 were added. The amendment filed 30 July 2007 has been entered. New claim 38 was added.

Applicant's election without traverse of species SEQ ID NO:4 (residues 131-163 of SEQ ID NO:1) and amino acid substitutions species Phe142Ala, Val144Thr and Tyr145Pro in the reply filed on 20 July 2007 is acknowledged. Applicant submits that claims 1, 21, 24, 25, 28, 29 read on the elected species.

The elected species has been rejected under 35 USC 112, First Paragraph, Enablement (see below). The Examiner is not obligated to extend the search and examination when the elected or subsequent species is rejected under *any* of 35 USC 101, 102, 103 or 112 1st, paragraph.

Claims 22, 23, 26, 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 20 July 2007. Claims 1, 21, 24, 25, 28-38 are under examination and are examined to the degree that they reflect the elected invention and no other embodiments.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 21, 24, 25, 28-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification states that the invention is concerned with the identification of epitopes for T-cell in human erythropoietin (EPO) (page 1). A sustained antibody response to a therapeutic protein such as EPO requires the stimulation of T helper cell proliferation and activation (page 2). The objective of the invention is to provide EPO analogues in which mapped T cell epitopes are compromised in their ability to function as MHC class II ligands and/or activate T cell in combination with MHC class II molecules (page 7). The specification states that the invention relates to using a panel of synthetic peptides in a T cell assay to map the immunogenic region of human EPO. Construction of a T cell epitope map of EPO protein is done by incubating peripheral blood mononuclear cells (PBMC; isolated from healthy donors) with the synthetic peptide immunogens. The PBMC preparation contains physiologic ratios of T cell to antigen present cells (APC). *In vitro* antigen stimulation is measured and EPO

derived peptide sequences able to evoke a T cell stimulation/proliferation index greater than 2 are used. The purpose of the invention is to provide an EPO molecule where the immunogenic regions that were mapped using a T cell assay are then modified such that upon re-testing in a T cell assay, the modified protein evokes a stimulation index smaller than the parental non-modified molecule. The modified EPO molecule should be substantially non-immunogenic or less immunogenic than any non-modified EPO molecule having the same biological activity when used in vivo (pages 7-8). The specification states that mapping T cell epitopes in the EPO sequence using the T cell proliferation assay resulted in the identification of three immunogenic regions R1, R2 and R3 (page 26, lines 15-20). The specification states that multiple amino acid substitutions to achieve elimination of MHC class binding in EPO were made based on computational methods (page 28). **The purported novelty is a modified EPO molecule, which has the same EPO activity as the non-modified EPO molecule but is less immunogenic when used *in vivo*.**

The instant claims are not supported by an enabling disclosure because the specification fails to teach that the suggested multiple amino acid substitutions in EPO achieved elimination of MHC class binding (i.e. evoked a T cell stimulation/proliferation index smaller than the parental non-modified EPO molecule). Stickler et al. (Journal of Immunotherapy 23(6):654-660, 2000) teach that epitope mapping of proteins is performed in vitro by measuring the proliferative responses of T cells presented with defined peptide molecules. Stickler et al. teach that several software programs have been made available that use the accumulated data from T cell mapping and HLA

binding peptide information to predict HLA binding epitopes in proteins of interest. Stickler et al. state that despite their power and accuracy, they only predict HLA binding, and thus the suggested epitopes for a given protein must be validated using in vitro T cell stimulatory assays (page 654, last paragraph-page 655). Stickler et al. teach the region around the E05/06 peptide as the major T cell epitope in a bacterial subtilisin protein based on the level of stimulation indices. The epitope in bacterial subtilisin was mutated and then re-tested using in vitro T cell stimulatory assay. Stickler et al. teach that some mutation changes in the sequence appear to have greatly interfered with the peptide's ability to induce a proliferative response. However, changing certain residues in the sequence caused an up-regulation in the in vitro T cell stimulatory assay (Figure 3). Stickler et al. teach that this phenomenon is not uncommon and points to the potential for changes in immunogenic when manipulating protein molecules to change their functions. Stickler et al. teach that predicted results must always be validated because HLA binding is necessary but not sufficient to define a fully functionally T cell epitope. A functional epitope includes residues that can be recognized by a T cell receptor of the correct specificity and with an appropriate binding affinity (page 658).

Secondly, the instant specification fails to teach that the modified EPO molecules have the same biological activity as non-modified EPO. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or

regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites (see Wells, 1990, Biochemistry 29:8509-8517; Ngo *et al.*, 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 433-440 and 492-495). Although the instant specification outlines procedures (via literature, software programs, etc) for mapping active EPO muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. For sequences having one or two substitutions, for example, the artisan would reasonably expect that many of the possible variants would retain functional properties comparable to those of the unmodified protein, and it would require only routine manipulations to make and test a reasonably representative sampling of the possible variants. However, as the number of modified sites increases (**as recited in the instant claims**), the number of possible EPO variants, and hence the degree of experimentation required, increases exponentially. Additionally, as plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The substitution of non-essential residues can often make the protein differ substantially. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically

large number of possible structural variants had the functional properties of the claimed proteins.

Due to the large quantity of experimentation necessary to generate the infinite number of EPO derivatives recited in the claims and screen same for a T cell stimulation/proliferation index that is smaller than the parental non-modified EPO molecule but has the same biological activity when used *in vivo* activity as the parental non-modified EPO molecule, the absence of working examples directed to same, the complex nature of the invention, the state of the art which establishes the unpredictability of the effects of mutation on protein structure/function and the importance of using in vitro T cell stimulation/proliferation assays to screen modified peptides, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Art of Record

The art made of record and not relied upon is considered pertinent to Applicant's disclosure. WO 99/03887 teach substitutions made in SEQ ID NO:4 (residues 131-163 of SEQ ID NO:1) of human erythropoietin (EPO). See page 3, line 26-page 4, line 3 and pages 31-37. However, WO 99/03887 fails to teach a loss of immunogenicity in the modified EPO molecule (i.e. exhibits a stimulation index smaller than the parental non-modified molecule when tested in a human T cell proliferation assay) and thus cannot be considered prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
9/18/07

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER

AU1647

9/27/07